Pharmacogenomics of Immunosuppression

Where do we stand?

Hussein Sheashaa, MD, FACP

Professor of Nephrology, Urology and Nephrology Center and Director of Medical E-Learning Unit, Mansoura University and Executive Director of ESNT- Virtual Academy: http://lms.mans.edu.eg/esnt/

MNDU, March 16th, 2016

Urology and Nephrology Center

http://lms.mans.ed[illegible]

Electronic Nephrology Education: ESNT Virt

Course categories:

Conferences and Meetings

2016

Conferences and Meetings / 2016

6th Annual MNDU (Nephro-Mans 2016

Day 1. Tuesday 15 March 2016

- Renal Biomarkers of Cardio-Renal Syndrome Dr. Mostafa Abdel Salam Mohamed
- Nutrition support in CKD patients Dr. Noha Abdelsalam
- A Focus on CKD and Heart Diseases Dr. Mohammed Kamal Nassar
- Management of Dyslipidemia in CKD Prof. Megahed Abuelmagd
- Diabetic Nephropathy Why why not Dr. Alaa Wafa
- Non diabetic kidney diseases in dibetic Prof. Ghada El-Kanishy
- IMMUNOSUPPRESSION Prof. M. A. Bakr
- Hepatitis C and Kidney Dr. Mostafa Anis Mohamed
- Thrombotic Microangiopathy Prof. Salwa Ibrahim
- Antidiabetic Drugs in Patients with Chronic Kidney Disease Prof. Ashraf Talaat

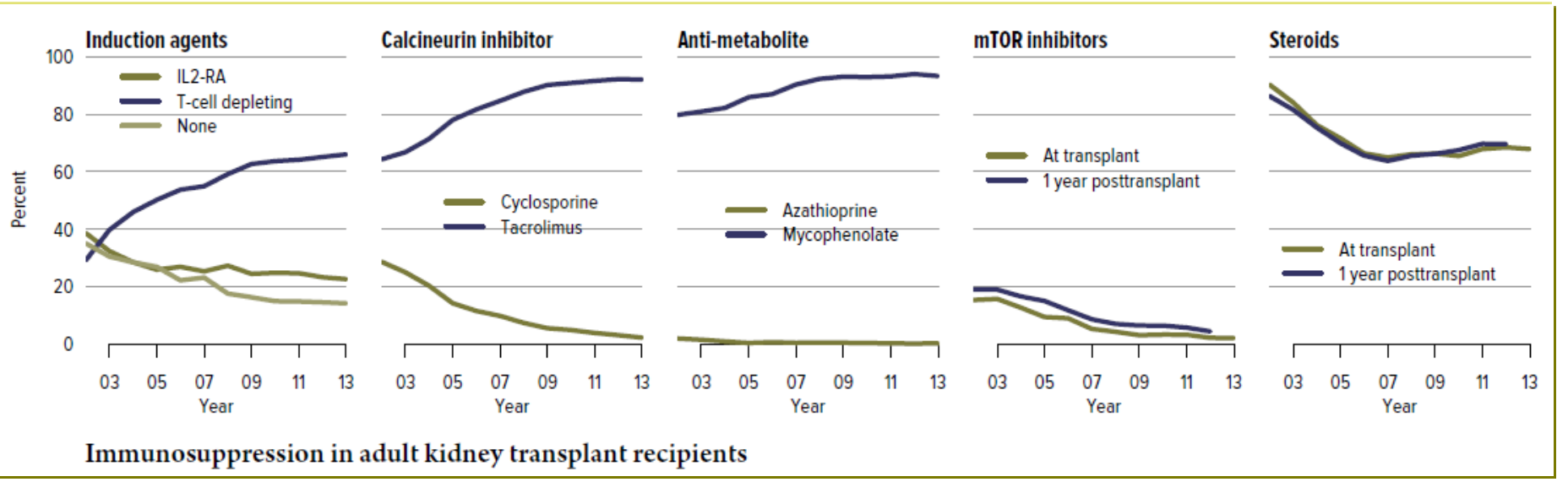
Day 2. Wednesday16 March 2016

- Pharmacogenomics of Immunosuppression. Prof.

Focus of The Talk

- Introduction and definitions
- CYP polymorphism
- ABCB polymorphism
- Other aspects
- Conclusion

Immunosuppression

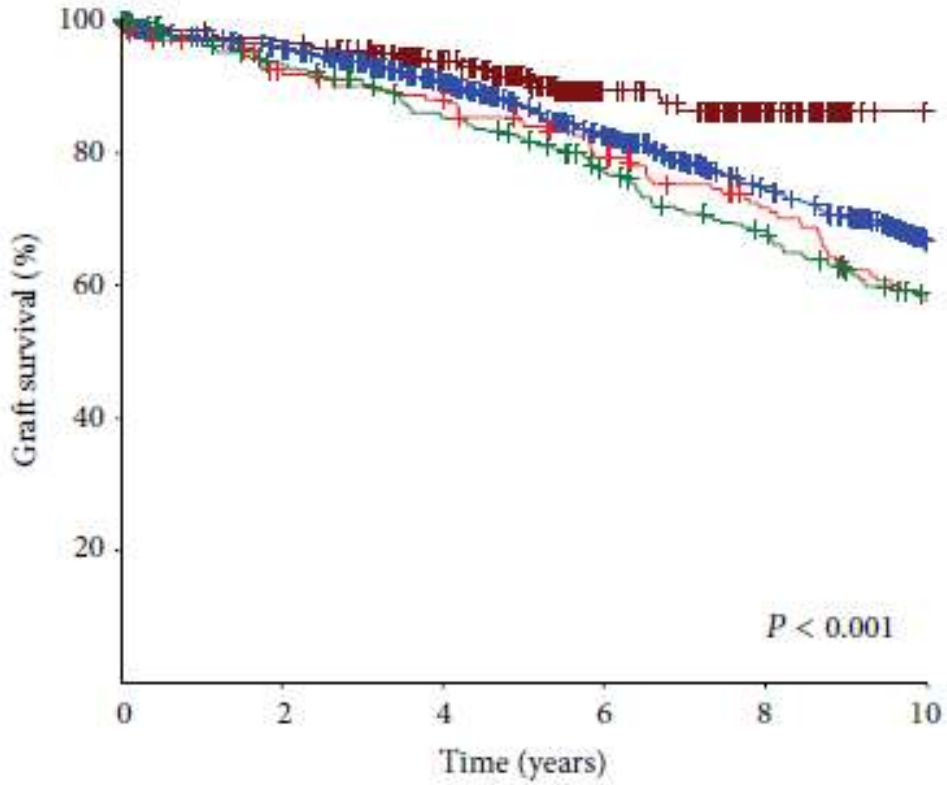


Immunosuppression in adult kidney transplant recipients

American Journal of Transplantation 2015;Jan
Special Issue: OPTN/SRTR 2013 Annual Data Report

Immunosuppression: Mansoura Experience

Urology and Nephrology Center



	5-year	10-year
Tac-based triple therapy	91.6	86.2
CsA-based triple therapy	86.9	66.5
CsA. based dual therapy	84.8	57.8
AZA-based dual therapy	82.2	58.3

Hindawi Publishing Corporation
BioMed Research International
Volume 2015, Article ID 912413, 9 pages
http://dx.doi.org/10.1155/2015/912413

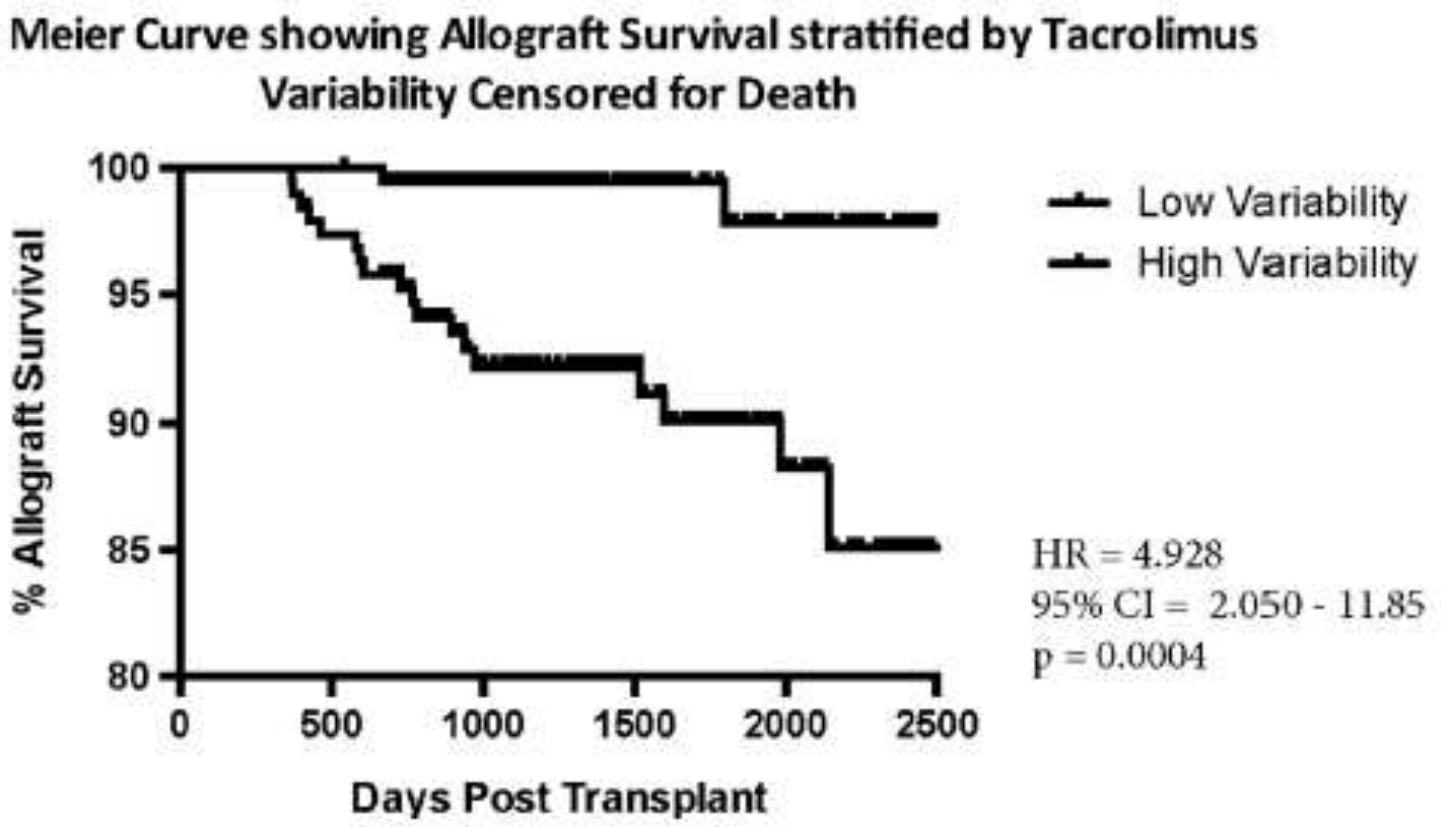
Research Article

Factors Affecting Graft Survival among Patients Receiving Kidneys from Live Donors: A Single-Center Experience

Mohamed A. Ghoneim,[1] Mohamed A. Bakr,[2] Ayman F. Refaie,[2] Ahmed I. Akl,[2] Ahmed A. Shokeir,[1] Ahmed B. Shehab El-Dein,[1] Hesham M. Ammar,[2] Amani M. Ismail,[3] Hussein A. Sheashaa,[2] and Mahmoud A. El-Baz[4]

[1] *Department of Urology, The Urology & Nephrology Center, Mansoura, Egypt*
[2] *Division of Nephrology, The Urology & Nephrology Center, Mansoura, Egypt*
[3] *Division of Immunology, The Urology & Nephrology Center, Mansoura, Egypt*
[4] *Division of Pathology, The Urology & Nephrology Center, Mansoura, Egypt*

Tacrolimus Levels: Variability



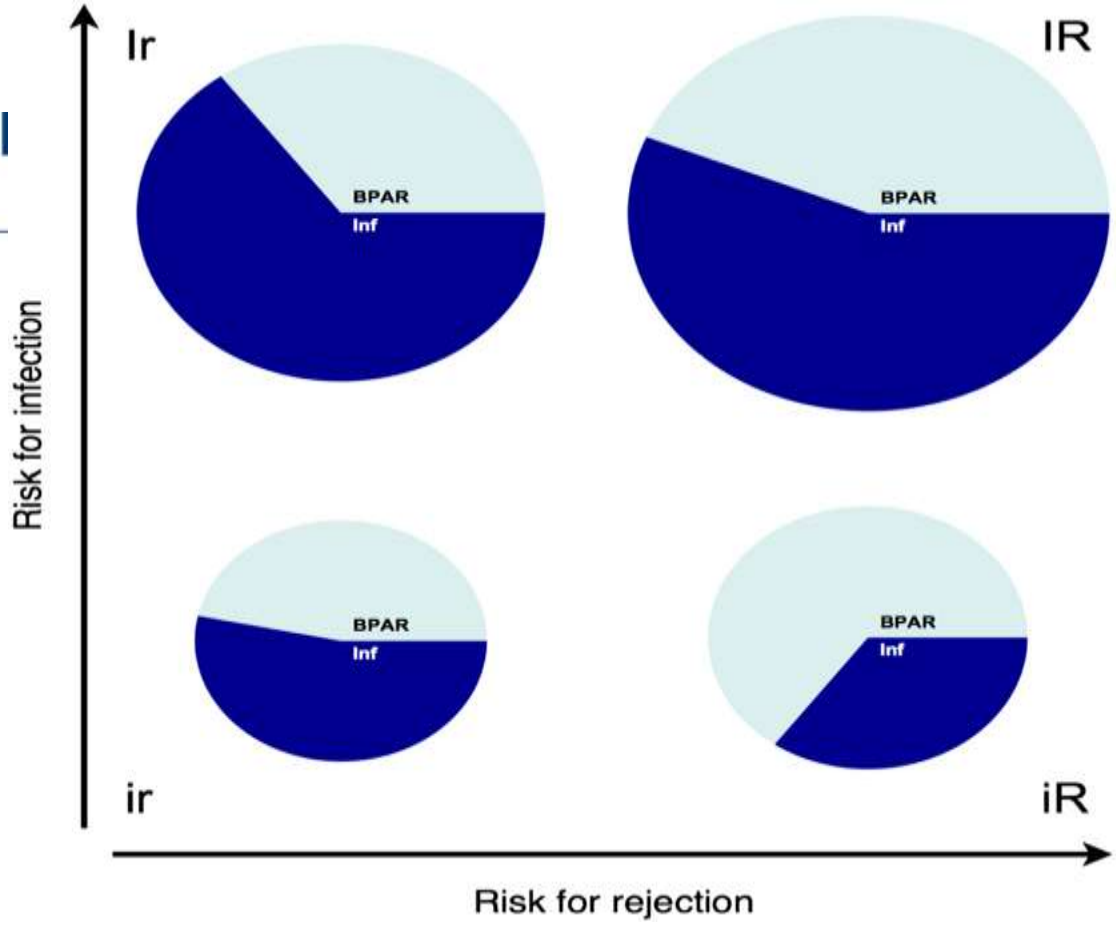
Transplantation 2016; in press

Risk Stratification

Urology and Nephrology Center

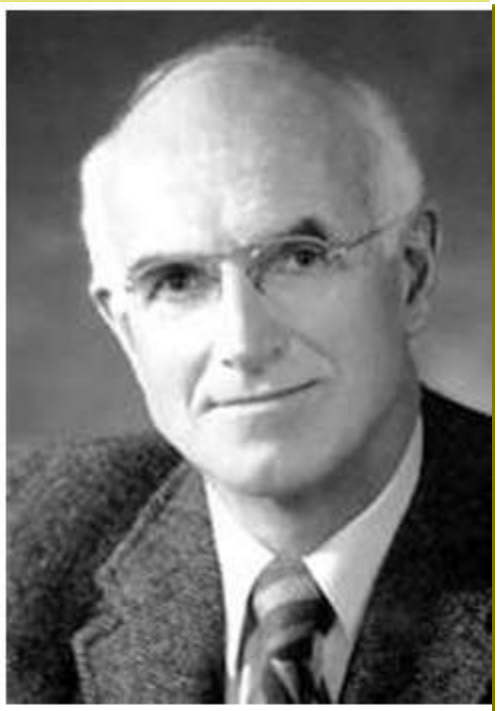
Article

Risk Stratification for Rejection and Infection after Kidney Transplantation



Clin J Am Soc Nephrol 10: 2213–2220, 2015.

Personalized Medicine: Genetics



Joseph E. Murray

Pharmacogenomics

Urology and Nephrology Center

Editorial

Personalized Medicine in Kidney Transplantation: In Our Lifetime?

Roslyn B. Mannon, M.D.
Division of Nephrology, Department of Medicine, and Division of Transplantation, Department of Surgery, Comprehensive Transplant Institute, University of Alabama, Birmingham, Alabama

Volume 14 • Number 5 • November 2015

NephSAP®
Nephrology Self-Assessment Program

Transplantation
Co-Editors:
John P. Vella, MD
Alexander C. Wiseman, MD

- In the 2015 State of the Union Address, President Barak Obama unveiled his “Precision Medicine Initiative.”

Pharmacogenomics: The Effect on Immunosuppression Management

Nephrology Self-Assessment Program - Vol 14, No 5, November 2015

Pharmacogenomics

- Pharmacogenomics refers to the relation between the human genetic profile and individual differences in clinical drug response.
- The aim of pharmacogenomics is to optimize treatment outcome and individualize therapy

Clinical Applications for Next-Generation Sequencing. http://dx.doi.org/10.1016/B978-0-12-801739-5.00011-8

Pharmacogenomics

Urology and Nephrology Center

CHAPTER

NEXT GENERATION SEQUENCING IN PHARMACOGENOMICS

11

Urszula Demkow

Department of Laboratory Diagnostics and Clinical Immunology of Developmental Age, Medical University of Warsaw, Warsaw, Poland

Pharmacogenomics

Urology and Nephrology Center

CHAPTER

Pharmacogenomics aspect of immunosuppressant therapy

5

Loralie Langman[1], Teun van Gelder[2], and Ron H.N. van Schaik[3]

[1]Department of Laboratory Medicine and Pathology, Mayo Clinic College of Medicine, Rochester, MN, USA; [2]Departments of Internal Medicine and Hospital Pharmacy, Erasmus University Medical Center, Rotterdam, Netherlands; [3]European Specialist Laboratory Medicine, Department of Clinical Chemistry, Erasmus University Medical Center, Rotterdam, Netherlands

M. Oellerich & A. Dasgupta (2016 Eds): Personalized Immunosuppression in Transplantation.

Pharmacogenomics:

Metabolism and Transport

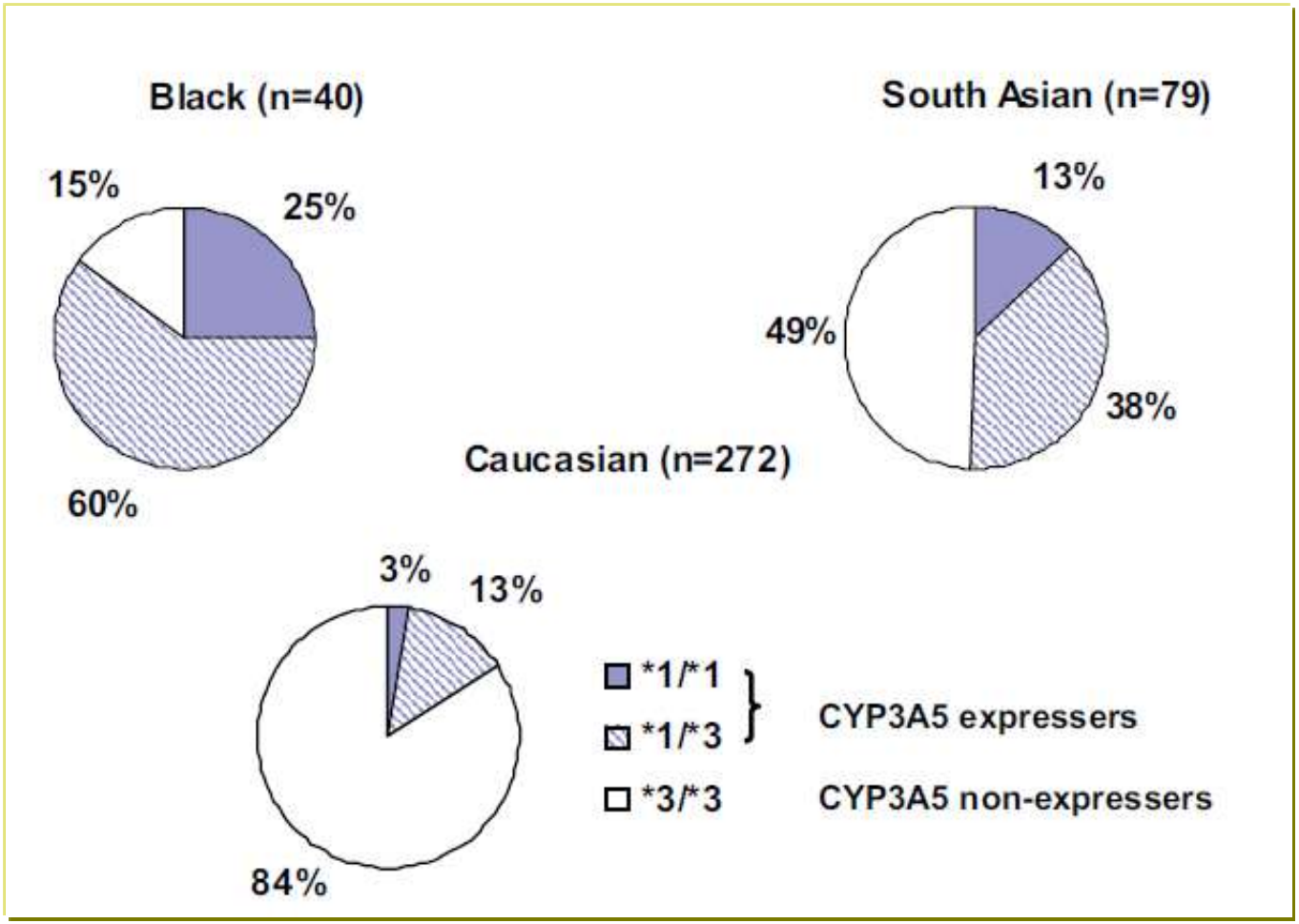
Urology and Nephrology Center

Drug Metabolism and Transport Genes

Cytochrome P450 Genes		Transporters	Others	
CYP11A1	*CYP2E1*	*ABCB1*	*SLC22A5*	*UGT1A1*
CYP11B1	*CYP2A4*	*ABCC2*	*SLC10A1*	*UGT1A4*
CYP11B2	*CYP2F1*	*ABCC3*	*SLC10A2*	*UGT2B7*
CYP19A1	*CYP2J2*	*ABCC4*	*SLC15A1*	*POR*
CYP1A1	*CYP2S1*	*ABCC5*	*SLC15A2*	*SLC28A1*
CYP26A1	*CYP2W1*	*ABCC6*	*SLC16A1*	*SLC38A1*
CYP27B1	*CYP3A43*	*ABCG2*	*SLC22A11*	*SLC47A1*
CYP2A13	*CYP3A5*		*SLC22A12*	*SLC47A2*
CYP2A6	*CYP3A7*		*SLC22A2*	*SLCO1A2*
CYP2B6	*CYP4A11*		*SLC22A4*	*SLCO1B1*
CYP2C18	*CYP4B1*		*SLC22A6*	*SLCO2B1*
CYP2C19	*CYP4F2*		*SLC22A7*	*SLCO4C1*
CYP2C8	*CYP4F22*		*SLC22A8*	*OSTalpha*
CYP2C9	*CYP7A1*			*OSTbeta*
CYP2D6	*CYP7B1*			
CYP8B1				

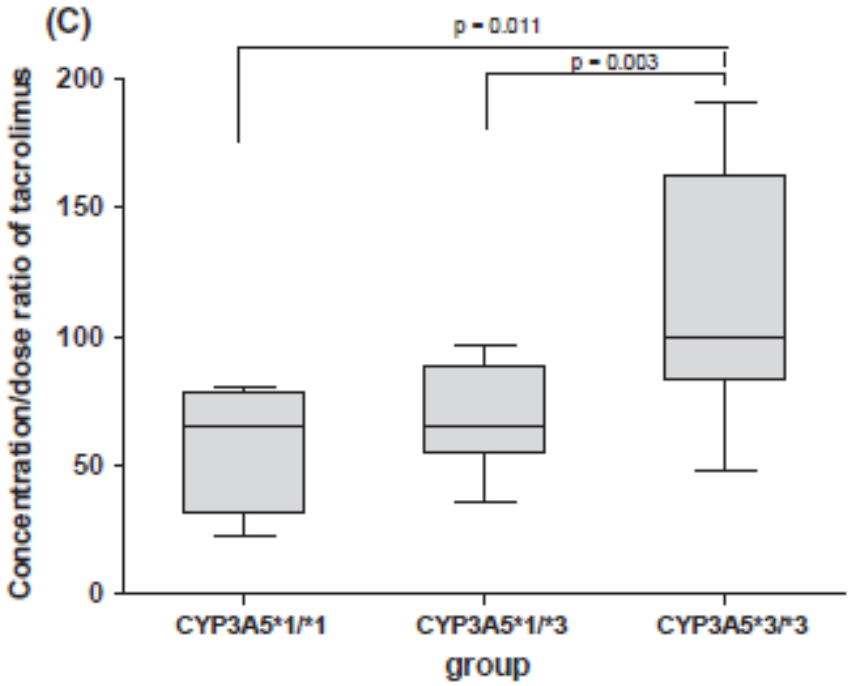
Clinical Applications for Next-Generation Sequencing. http://dx.doi.org/10.1016/B978-0-12-801739-5.00011-8

CYP3A5

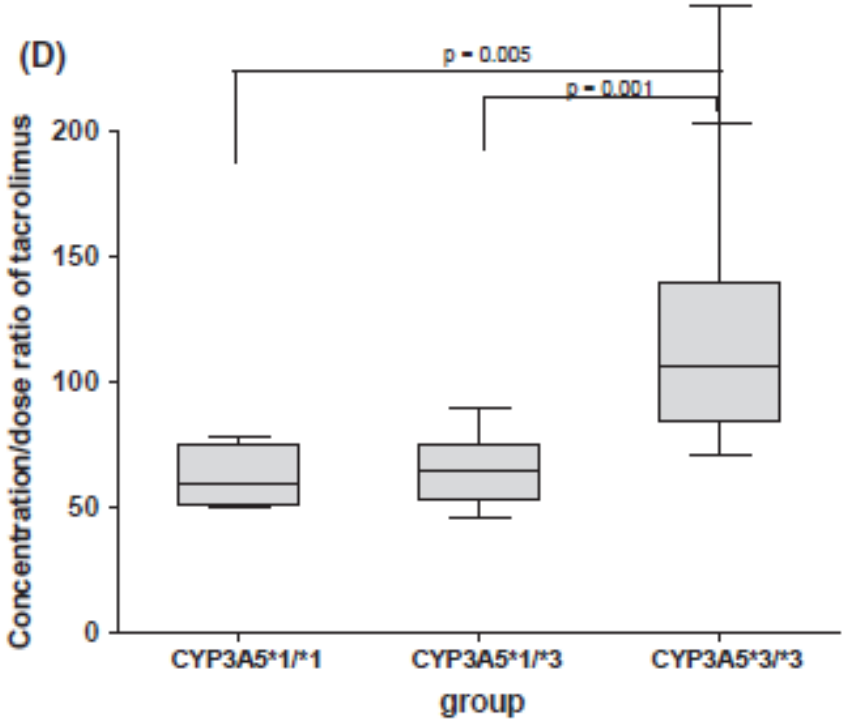


Transplantation 2008;85: 163–165 . Review

CYP3A5



6m



12m

Int J Clin Pract, May 2015, 69 (Suppl. 183), 16–22

Tacrolimus:
DNA Microarray

The Pharmacogenomics Journal (2016), 1–6

www.nature.com/tpj

ORIGINAL ARTICLE

A pharmacogenomic study on the pharmacokinetics of tacrolimus in healthy subjects using the DMET™ Plus platform

Y Choi[1,5], F Jiang[1,5], H An[1,2], HJ Park[3], JH Choi[3] and H Lee[1,4]

CYP3A5 and Tacrolimus: RCT (62:58)/ Diltiazem

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Individualization of tacrolimus dosage basing on cytochrome P450 3A5 polymorphism – a prospective, randomized, controlled study

Clin Transplant 2013: 27: E272–E281

CYP3A5 and Tacrolimus:
Liver Transplantation

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TABLE 5. Difference in Tacrolimus C_0/Dose Ratio in Paired Donor and/or Recipient Expressers of CYP3A5 (Group 1) Versus Paired Donor and Recipient Nonexpressers (Group 2)

Time After Transplant	Group 1 Paired Genotype (Donor:Recipient)	Group 2 Paired Genotype (Donor:Recipient)	No. Studies Included	n	WMD	95% Confidence Interval	I_2, %
7 d*	*1/*1 or *1/*3:*3/*3	*3/*3:*3/*3	2	56	−1.968	−4.283 to 0.347	91
14 d*	*1/*1 or *1/*3:*3/*3	*3/*3:*3/*3	2	56	−1.133	−1.861 to 0.405	33
1 mo*	*1/*1 or *1/*3:*3/*3	*3/*3:*3/*3	2	56	−1.076	−1.659 to 0.493	0
2 mo*	*1/*1 or *1/*3:*3/*3	*3/*3:*3/*3	1	36	−2.124	−2.981 to 1.266	NA
3 mo*	*1/*1 or *1/*3:*3/*3	*3/*3:*3/*3	1	36	−2.394	−3.291 to 1.497	NA
6 mo*	*1/*1 or *1/*3:*3/*3	*3/*3:*3/*3	1	36	−3.688	−4.806 to 2.571	NA
12 mo*	*1/*1 or *1/*3:*3/*3	*3/*3:*3/*3	1	36	−3.266	−4.307 to 2.226	NA
Sub total					−1.933	−2.573 to 1.293	79
7 d‡	*3/*3:*1/*1 or *1/*3	*3/*3:*3/*3	2	53	−0.866	−1.546 to 0.186	12
14 d‡	*3/*3:*1/*1 or *1/*3	*3/*3:*3/*3	2	53	−1.840	−4.506 to 0.826	92
1 mo‡	*3/*3:*1/*1 or *1/*3	*3/*3:*3/*3	2	53	−1.337	−3.330 to 0.656	88
2 mo‡	*3/*3:*1/*1 or *1/*3	*3/*3:*3/*3	1	30	−2.789	−3.943 to 1.634	NA
3 mo‡	*3/*3:*1/*1 or *1/*3	*3/*3:*3/*3	1	30	−2.247	−3.318 to 1.177	NA
6 mo‡	*3/*3:*1/*1 or *1/*3	*3/*3:*3/*3	1	30	−4.306	−5.746 to 2.867	NA
12 mo‡	*3/*3:*1/*1 or *1/*3	*3/*3:*3/*3	1	30	−2.574	−3.694 to 1.454	NA
Sub total					−1.942	−2.724 to 1.161	83

*Donor *1/*1 or *1/*3 genotype and recipient *3/*3 genotype compared with donor *3/*3 genotype and recipient *3/*3 genotype.
†Donor *1/*1 or *1/*3 genotype and recipient *1/*1 or *1/*3 genotype compared with donor *3/*3 genotype and recipient *3/*3 genotype.
‡Donor *3/*3 genotype and recipient *1/*1 or *1/*3 genotype compared with donor *3/*3 genotype and recipient *3/*3 genotype.
I_2, percentage of total variation across studies; NA, not available; WMD, weighted mean differences in tacrolimus C0/dose values.

Ther Drug Monit 2014;36:442–447)

CYP3A5 and Everolimus:
Cardiac Transplantation

Urology and Nephrology Center

DNG

Influence of *CYP3A5* genetic variation on everolimus maintenance dosing after cardiac transplantation

Lesche D, Sigurdardottir V, Setoud R, Englberger L, Fiedler GM, Largiadèr CR, Mohacsi P, Sistonen J. Influence of *CYP3A5* genetic variation on everolimus maintenance dosing after cardiac transplantation.

Dorothea Lesche[a,b], Vilborg Sigurdardottir[c], Raschid Setoud[c], Lars Englberger[d], Georg M. Fiedler[a], Carlo R. Largiadèr[a], Paul Mohacsi[c] and Johanna Sistonen[a]

[a]Institute of Clinical Chemistry, University Hospital (Inselspital Bern), University of Bern, [b]Graduate School for Cellular and Biomedical Sciences, University of Bern; Departments of [c]Cardiology and [d]Cardiovascular Surgery, Swiss Cardiovascular Centre, University Hospital (Inselspital Bern), Bern, Switzerland

Clin Transplant 2015: 29: 1213–1220

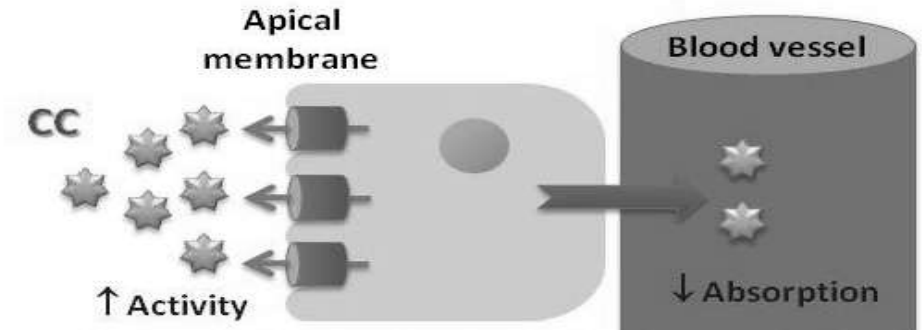
CYP2E1 and Rejection:
n (63 AR, 284 no AR)

Association studies of cytochrome P450, family 2, subfamily E, polypeptide 1 (*CYP2E1*) gene polymorphisms with acute rejection in kidney transplantation recipients

OR: 2.6 (1.43-4.77)

Clin Transplant 2014: 28: 707–712

ABCB1 GP



- Functional activity of glycoprotein-P in the transport of tacrolimus in the intestine epithelium.

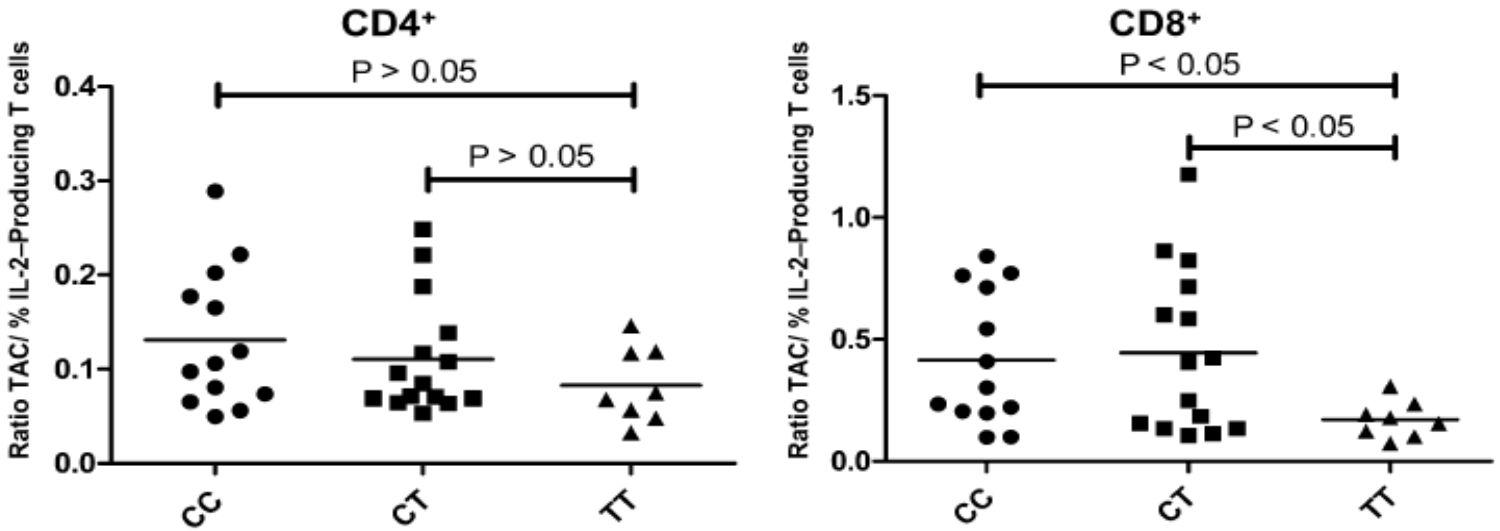
Renal Transplantation – Updates And Advances Textbook, 2012

ABCB1 and Pharmacodynamics of Tacrolimus

Urology and Nephrology Center

ORIGINAL ARTICLE

Genetic Polymorphisms in ABCB1 Influence the Pharmacodynamics of Tacrolimus



Ther Drug Monit 2013;35:459–465

ABCB1 Genetic Polymorphisms

CLINICAL RESEARCH www.jasn.org

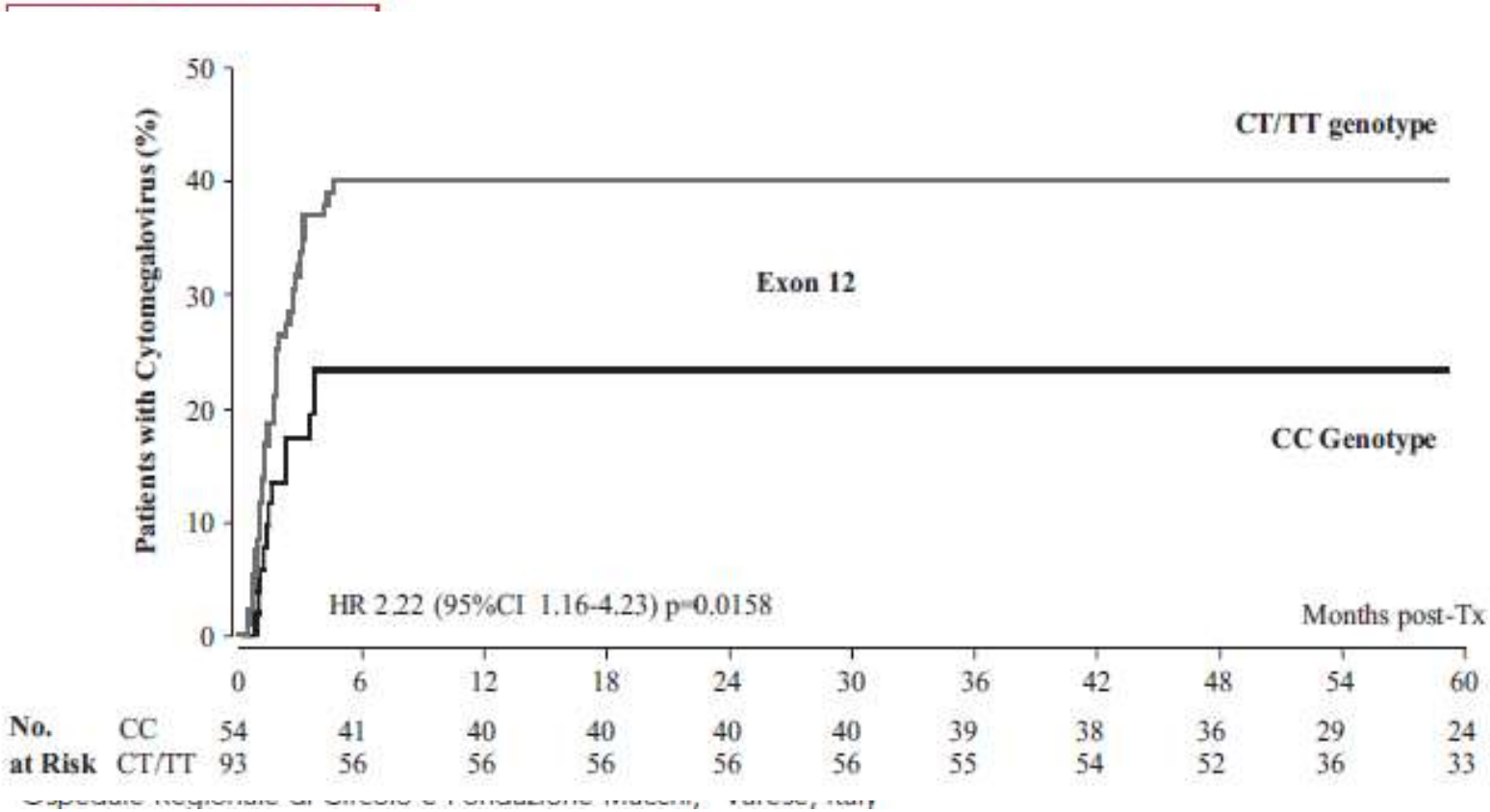
Donor *ABCB1* Variant Associates with Increased Risk for Kidney Allograft Failure

Jason Moore,*† Amy Jayne McKnight,‡ Bernd Döhler,§ Matthew J. Simmonds,‖ Aisling E. Courtney,‡ Oliver J. Brand,‖ David Briggs,¶ Simon Ball,*†† Paul Cockwell*†† Christopher C. Patterson‡ Alexander P. Maxwell,‡ Stephen C.L. Gough,‖ Gerhard Opelz,§ and Richard Borrows*††

*Department of Nephrology and Transplantation, Queen Elizabeth Hospital, Birmingham, United Kingdom; †The Kidney Unit, Royal Devon and Exeter NHS Foundation Trust, Wonford Hospital, Exeter, United Kingdom; ‡Nephrology Research Group, Queen's University of Belfast, Northern Ireland, United Kingdom; §Collaborative Transplant Study Group, University of Heidelberg, Heidelberg, Germany; ‖Oxford Centre for Diabetes, Endocrinology and Metabolism, University of Oxford, Churchill Hospital, Oxford, United Kingdom; ¶National Blood Service, Birmingham, United Kingdom; and ††Centre for Translational Inflammation Research, University of Birmingham, Birmingham, United Kingdom

J Am Soc Nephrol 23: 1891–1899, 2012.

ABCB1 Genetic Polymorphisms



J Am Soc Nephrol 20: 1404–1415, 2009.

CYP3A4 and CsA: 50 Egyptian Patients

Mol Biol Rep (2015) 42:105–117
DOI 10.1007/s11033-014-3747-8

Impact of CYP3A4 and MDR1 gene (G2677T) polymorphisms on dose requirement of the cyclosporine in renal transplant Egyptian recipients

Ola Sharaki · Montasser Zeid · Pacint Moez · Nermine Hossam Zakaria · Eman Nassar

Alexandria University

KCNQ1 and Tacrolimus:
PTDM (145/260)

KCNQ1 gene variants and risk of new-onset diabetes in tacrolimus-treated renal-transplanted patients

CC genotype: OR: 1.8 (1.14-2.93)

Clin Transplant 2011: 25: E284–E291

CRTC2:
Post-transplant MS

Urology and Nephrology Center

DNG

ORIGINAL ARTICLE

CRTC2 polymorphism as a risk factor for the incidence of metabolic syndrome in patients with solid organ transplantation

L Quteineh[1], P-Y Bochud[2], D Golshayan[3], S Crettol[1], J-P Venetz[3], O Manuel[2,3], Z Kutalik[4,5], A Treyer[1], R Lehmann[6], NJ Mueller[7], I Binet[8], C van Delden[9], J Steiger[10], P Mohacsi[11], J-f Dufour[12], PM Soccal[13], M Pascual[3], CB Eap[1,14] and The Swiss Transplant Cohort Study[15]

The CREB-regulated transcription co-activator 2

The Pharmacogenomics Journal advance online publication, 8 December 2015

Gene Polymorphism

Letters to the Editor

β Cell Glucotoxic-Associated Single Nucleotide Polymorphisms in Impaired Glucose Tolerance and New-Onset Diabetes After Transplantation

SNPs (rs10484821, rs11580170, rs1836882, rs198372, rs2020902, rs2861484, rs4394754, rs7533125)

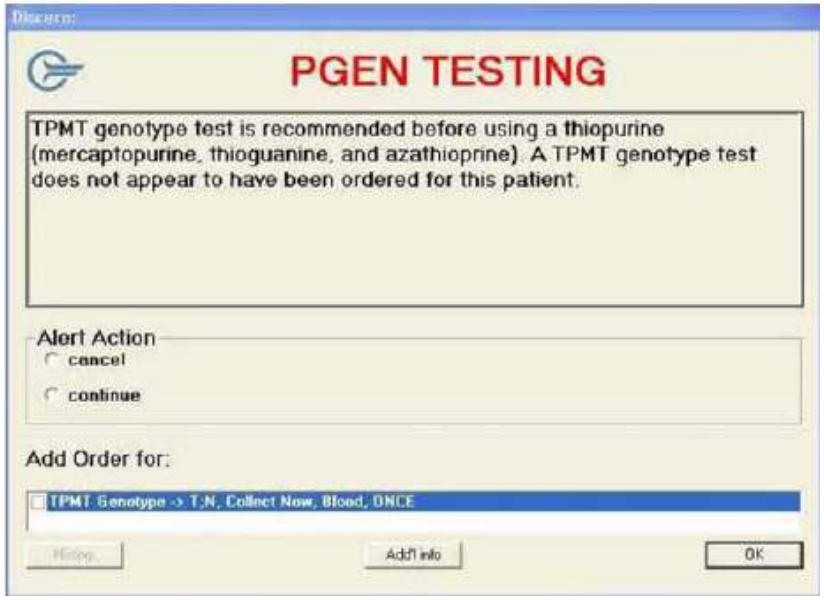
Transplantation & Volume 98, Number 3, August 15, 2014

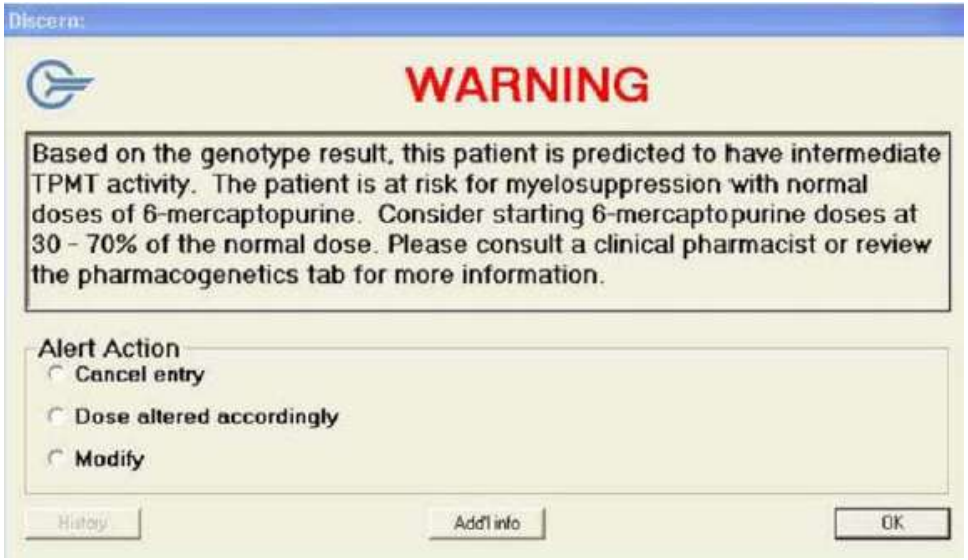
Preemptive Pharmacogenomics

Urology and Nephrology Center

Research and applications

Development and use of active clinical decision support for preemptive pharmacogenomics



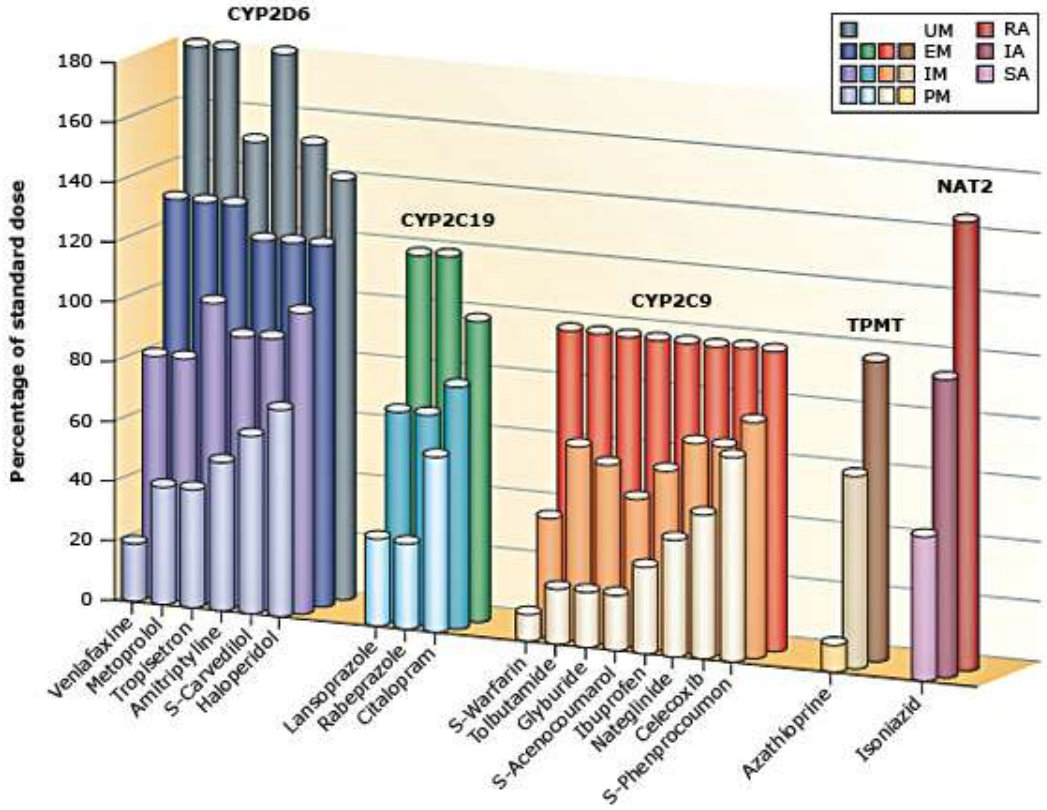


J Am Med Inform Assoc 2014;21:e93–e99.

TPMT

Urology and Nephrology Center

Examples of dose adjustments based on PGDx

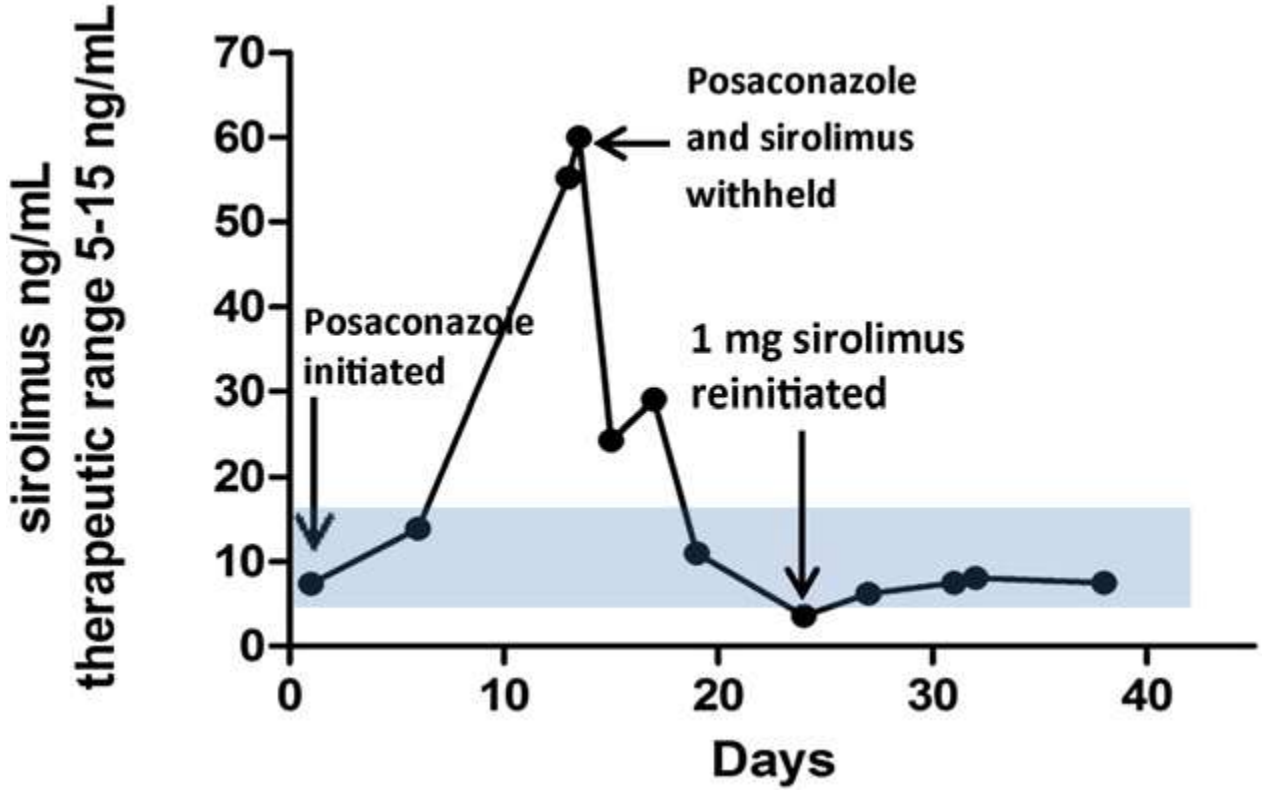


Nat Rev Drug Discov 2005; 4:639.

Sirolimus Pharmacogenetics:

Drug Efficacy and Toxicity

CYP3A4 extensive metabolizer



Clinica Chimica Acta 450 (23 October 2015) 15–18

Mycophenolic Acid AUC:

UGT2B7

Urology and Nephrology Center

Pharmacogenomics and Personalized Medicine

Dovepress
open access to scientific and medical research

Open Access Full Text Article

ORIGINAL RESEARCH

Mycophenolic acid AUC in Thai kidney transplant recipients receiving low dose mycophenolate and its association with *UGT2B7* polymorphisms

This article was published in the following Dove Press journal:
Pharmacogenomics and Personalized Medicine
5 December 2014
Number of times this article has been viewed

Pharmacogenetics: Tacrolimus Scenario

Urology and Nephrology Center

Dosing recommendations for tacrolimus based on *CYP3A5* phenotype

CYP3A5 phenotype[a]	Implications for tacrolimus pharmacologic measures	Therapeutic recommendations[b]	Classification of recommendations[c]
Extensive metabolizer (CYP3A5 expresser)	Lower dose-adjusted trough concentrations of tacrolimus and decreased chance of achieving target tacrolimus concentrations.	Increase starting dose 1.5–2 times recommended starting dose.[d] Total starting dose should not exceed 0.3 mg/kg/day. Use therapeutic drug monitoring to guide dose adjustments.	Strong
Intermediate metabolizer (CYP3A5 expresser)	Lower dose-adjusted trough concentrations of tacrolimus and decreased chance of achieving target tacrolimus concentrations.	Increase starting dose 1.5–2 times recommended starting dose.[a] Total starting dose should not exceed 0.3 mg/kg/day. Use therapeutic drug monitoring to guide dose adjustments.	Strong
Poor metabolizer (CYP3A5 nonexpresser)	Higher ("normal") dose-adjusted trough concentrations of tacrolimus and increased chance of achieving target tacrolimus concentrations.	Initiate therapy with standard recommended dose. Use therapeutic drug monitoring to guide dose adjustments.	Strong

CLINICAL PHARMACOLOGY & THERAPEUTICS | VOLUME 98 NUMBER 1 | JULY 2015

Tacrolimus Scenario: RCT, 240 Patients

American Journal of Transplantation 2016; XX: 1–12
Wiley Periodicals Inc.

A Randomized Controlled Trial Comparing the Efficacy of *Cyp3a5* Genotype-Based With Body-Weight-Based Tacrolimus Dosing After Living Donor Kidney Transplantation

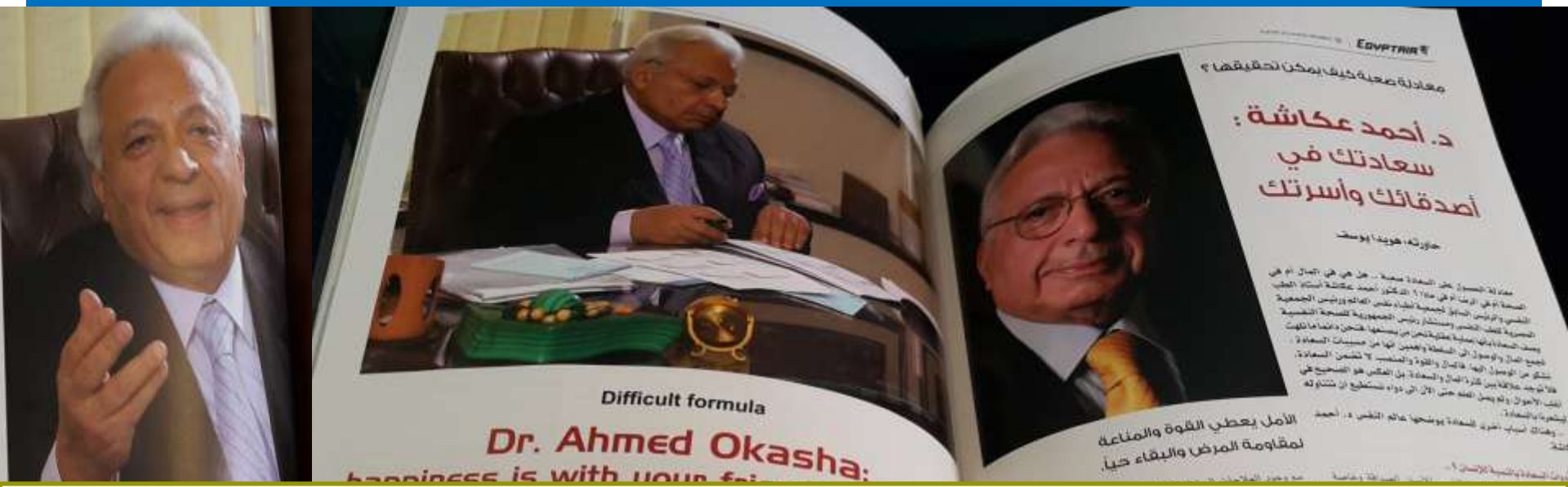
	Standard-dose group	Genotype-based group	*p*
	n = 99	n = 104	
Supra-therapeutic concentration	39 (39.4%)	31 (29.8%)	0.20
Therapeutic concentration	37 (37.4%)	37 (35.6%)	0.79
Sub-therapeutic concentration	23 (23.2%)	36 (34.6%)	0.10

Pharmacogenetics:

Limitations and Challenges

Urology and Nephrology Center

Urology and Nephrology Center



Hope is a good measure of Happiness